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REMARKS

I. Status of Claims

Upon entry of the present amendments, claims 99-110, 112-129, and 131-136 will be pending in this application. Claims 99-134 are finally rejected.

Applicants gratefully acknowledge the Examiner's favorable reconsideration and withdrawal of the previous 35 U.S.C. §102 rejection over Rambert et al., and the previous 35 U.S.C. § 103(a) rejections over Rambert et al. in view of Pitha et al., and over Rambert et al. in view of Pitha et al. and further in view of Grebow et al.

Claim 99 is amended to specifically recite particular diseases and disorders treated with the modafinil compound:cyclodextrin mixture of the present invention. Support for this amendment can be found on page 12, lines 16-23.

Claims 99 and 126 are amended to include the limitations of claims 111 and 130, respectively, which are now canceled. Amended claims 99 and 126 recite that the modafinil compound:cyclodextrin mixture provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

New claims 135 and 136 recite that the cyclodextrin masks the taste of the modafinil compound. Support for claims 135 and 136 can be found on page 4, lines 14-17.

No new matter has been added by way of these amendments.

II. Rejection under 35 U.S.C. §112 – Indefiniteness

Claims 99-116, 118, 121-132, and 134 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner alleges that it is impossible to determine a therapeutically effective amount of the modafinil compound:cyclodextrin mixture without knowing what disease is to be treated.

The amended claims specifically recite the disease or disorder to be treated. In view of these amendments, Applicants respectfully request that this rejection be withdrawn.

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III. Rejections under 35 U.S.C. §103(a)

Lafon in view of Rambert:

Claims 99-110, 112-120, 126-129, and 131-133 are rejected under 35 U.S.C. §103(a) as being obvious over Lafon (US 4,927,855) in view of Rambert et al. (Neuropharmacology, 1994). The Examiner alleges that Lafon teaches the administration of (-)modafinil for the treatment of hypersomnia, and Rambert teaches solubilizing modafinil with HP-β-cyclodextrin. The Examiner further alleges that is would have been obvious at the time of Applicant's invention to modify the method of Lafon to treat hypersomnia by orally administering the Rambert solution.

After careful consideration of the Examiner's position, Applicant's respectfully traverse this rejection. Applicants respectfully point out that the limitations of claims 111 and 130, which are not rejected, have been added to amended claims 99 and 126. As amended, claims 99 and 126 recite that the modafinil compound:cyclodextrin mixture provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

In view of the amendment of claims 99 and 126 to include the limitations of non-rejected claims 111 and 130, this rejection is moot. Applicants respectfully request that this rejection be withdrawn.

Lafon in view of Rambert and further in view of Loftsson:

Claims 99-110, 112-120, 126-129, and 131-133 are rejected under 35 U.S.C. §103(a) as being obvious over Lafon (US 4,927,855) in view of Rambert et al. (Neuropharmacology, 1994) and further in view of Loftsson et al. (J. Pharm. Sci., 1996). The Examiner alleges that Lafon teaches the administration of (-)modafinil for the treatment of hypersomnia, Rambert teaches solubilizing modafinil with HP-β-cyclodextrin, and Loftsson teaches numerous cyclodextrins for solubilization and increased bioavailability of drugs. The Examiner further alleges that is would have been obvious at the time of Applicant's invention to modify the method of Lafon to treat hypersomnia by orally administering modafinil solubilized with HP-β-cyclodextrin and the cyclodextrins of Loftsson.

After careful consideration of the Examiner's position, Applicant's respectfully traverse this rejection. Applicants respectfully point out that the limitations of claims 111 and 130, which are not rejected, have been added to amended claims 99 and 126. As amended, claims 99 and

126 recite that the modafinil compound:cyclodextrin mixture provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

In view of the amendment of claims 99 and 126 to include the limitations of non-rejected claims 111 and 130, this rejection is moot. Applicants respectfully request that this rejection be withdrawn.

Lafon in view of Rambert and further in view of Pitha:

Claims 99-134 are rejected under 35 U.S.C. §103(a) as being obvious over Lafon (US 4,927,855) in view of Rambert et al. (Neuropharmacology, 1994) and further in view of Pitha et al. (Int. J. Pharm., 1986). The Examiner alleges that Lafon teaches the administration of (-)modafinil for the treatment of hypersomnia, Rambert teaches solubilizing modafinil with HP-β-cyclodextrin, and Pitha teaches solubilizing drugs using 40-50% (w/w) 2-HP-β-cyclodextrin. The Examiner further alleges that is would have been obvious at the time of Applicant's invention to modify the method of Lafon to treat hypersomnia by orally administering modafinil solubilized with a concentrated solution of 2-HP-β-cyclodextrin.

After careful consideration of the Examiner's position, Applicant's respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. Neither Lafon nor Rambert nor Pitha teach or suggest a modafinil compound:cyclodextrin mixture that provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

A second requirement of a *prima facie* case of obviousness is that the prior art must provide a reasonable expectation of successfully achieving the invention. As currently amended, the claims recite that the modafinil compound:cyclodextrin mixture provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

As set forth in paragraph 6 of the accompanying declaration under 37 C.F.R. § 1.132 of Dr. Martin Jacobs, Loftsson teaches that predicting the aqueous solubility of a drug after cyclodextrin complexation is dependent upon the initial water solubility of the drug, and only drugs having an aqueous solubility in the micromole/L range (or lower) may be predicted to display large enhancements in aqueous solubility upon cyclodextrin complexation.

As set forth in paragraphs 7 and 8 of the accompanying declaration, the aqueous

solubility of modafinil is 0.4 mg/mL, which corresponds to 1.46 mmol/L. Surprisingly, the aqueous solubility of modafinil after complexation with 2-HP-β-cyclodextrin is at least 45 mg/mL, which corresponds to a relative solubility enhancement of 112.5 (45/0.4). Even at an aqueous solubility of 30 mg/mL, the relative solubility enhancement for modafinil is 75 (30/0.4).

As set forth in paragraphs 9-11 of the accompanying declaration, *none* of the eight (8) Pitha compounds having an aqueous solubility of at least 1.46 mmol/L (i.e., the aqueous solubility of modafinil) exhibited a solubility enhancement of 75 or more when mixed with 2-HP-β-cyclodextrin. Furthermore, only three (3) of the additional nine (9) compounds having a water solubility within an order of magnitude lower than modafinil (i.e., 146 μmol/L to 1.46 mmol/L) exhibited a relative solubility enhancement factor of 75 or more. Accordingly, Pitha would not provide a person of ordinary skill in the art with a reasonable expectation that HP-β-cyclodextrin would enhance the aqueous solubility of modafinil to 30 mg/mL (i.e., a relative solubility enhancement factor of 75), let alone to 45 mg/mL (i.e., a relative solubility enhancement of 112.5).

In view of the fact that the cited references do not teach or suggest a modafinil compound:cyclodextrin mixture that provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL, and the prior art does not provide a reasonable expectation of successfully preparing such a mixture, the claims are not *prima facie* obvious. Applicants respectfully request that this rejection be withdrawn.

Scammell in view of Rambert:

Claims 99-101, 103-107, 109-110, 112-115, 117-120, 126-129, and 131-133 are rejected under 35 U.S.C. §103(a) as being obvious over Scammell (US 6,455,588) in view of Rambert et al. (Neuropharmacology, 1994). The Examiner alleges that Scammell teaches the administration of modafinil for the stimulation of appetite and weight gain, and Rambert teaches solubilizing modafinil with HP-β-cyclodextrin. The Examiner further alleges that is would have been obvious at the time of Applicant's invention to modify the method of Scammell to orally administer modafinil solubilized with HP-β-cyclodextrin to stimulate appetite and promote weight gain.

After careful consideration of the Examiner's position, Applicant's respectfully traverse

this rejection. Applicants respectfully point out that:

> **U.S. Application Ser. No. 10/023,441 and U.S. Patent No. 6,455,588 were, at the time the invention of U.S. Application Ser. No. 10/023,441 was made, owned by Cephalon, Inc.**

In view of the common ownership of the present application and Scammell, pursuant to 35 U.S.C. § 103(c) Scammell is disqualified from use in a rejection under 35 U.S.C. § 103(a) against the claims of this application. Applicants respectfully request that this rejection be withdrawn.

IV. Double Patenting Rejection

Claims 99-101, 103-105, and 117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 16 of Scammell (US 6,455,588) in view of Rambert et al. (Neuropharmacology, 1994). The Examiner alleges that Scammell teaches the administration of modafinil for the stimulation of appetite and weight gain, and Rambert teaches solubilizing modafinil with HP-β-cyclodextrin. The Examiner further alleges that is would have been obvious at the time of Applicant's invention to modify the method of Scammell to orally administer modafinil solubilized with HP-β-cyclodextrin to stimulate appetite and promote weight gain.

After careful consideration of the Examiner's position, Applicant's respectfully traverse this rejection. Applicants respectfully point out that the limitations of claim 111, which was not rejected, have been added to amended claim 99. As amended, claim 99 recites that the modafinil compound:cyclodextrin mixture provides an aqueous solubility of the modafinil compound of at least about 30 mg/mL.

In view of the amendment of claim 99 to include the limitations of non-rejected claim 111, this rejection is moot. Applicants respectfully request that this rejection be withdrawn.

V. **Unexpected Results**

For at least the reasons cited above, Applicants respectfully submit that the present invention is not *prima facie* obvious in view of the cited references. However, even if one were to assume that the present invention was *prima facie* obvious, the *prima facie* case is rebutted by the showing of nonobviousness presented in the attached declaration under 37 C.F.R. § 1.132 by Dr. Martin Jacobs, in connection with all of the other evidence on record. The declaration is necessary to introduce new data (e.g., Tables 1-3 and Figure 1), and was not presented earlier because it addresses the new grounds of rejection contained in the November 21, 2005 Office Action.

Figure 1 and Table 2 of the declaration show the plasma levels of modafinil observed in rats after oral administration of three (3) different dosage forms: (a) modafinil dissolved in 95:5 (w/w) PEG400:benzyl alcohol, (b) modafinil suspended in Oraplus®, and (c) modafinil complexed with 2-HP-β-cyclodextrin. Pharmacokinetic data for the three (3) different dosage forms are presented in Table 3 of the declaration.

As set forth in the declaration at paragraph 19, the extent of modafinil absorption from the cyclodextrin solution was 4.6 times higher than the Oraplus® suspension and 5.9 times higher than the PEG400:benzyl alcohol solution. At the same time, the rate of modafinil absorption from the cyclodextrin solution was not substantially slower than from the Oraplus® suspension or the PEG400:benzyl alcohol solution (*see* declaration, paragraph 21).

As set forth in the declaration at paragraphs 12-22, it was not predictable at the time of the present invention that complexation of a modafinil compound with a cyclodextrin would substantially increase the *extent* of absorption without substantially decreasing the *rate* of absorption, especially as compared to a true modafinil solution in PEG400:benzyl alcohol. Accordingly, the oral bioavailability of the modafinil:2-HP-cyclodextrin complex is unexpected.

In view of the unexpected rate and extent of absorption of a modafinil compound when complexed with a cyclodextrin, the present invention is not obvious.

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VI. **Conclusion**

For at least the reasons set forth herein, Applicants respectfully submit that each rejection and objection has been addressed. It is believed that all the claims are in form for allowance, and an early notification to that end is respectfully requested. Applicants invite the Examiner to contact the undersigned at (610) 883-5679 to clarify any remaining issues.

Respectfully submitted,

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